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(54) **Medical treatment and apparatus therefor**

(57) A subcutaneously implantable diffusion chamber is proposed, the chamber housing hybrid living cells adapted to produce sub-cellular material capable of affording beneficial activity in the body for medical purposes and the chamber having a wall defined by a membrane which, in vivo, inhibits the free diffusion therethrough of the cells but not sub-cellular material. The cells can be of hybridoma form to produce monoclonal antibodies specific for tumours. The membrane acts to allow outward diffusion of the antibodies or other activie sub-cellular material, to allow inward diffusion from the host body of oxygen, nutrients or other sub-cellular material to sustain the cell effectiveness, and to inhibit outward diffusion of the cells and prevents metastasis as a neoplastic growth or other undesirable results. The membrane preferably only passes material of up to about 0.2µm diameter.

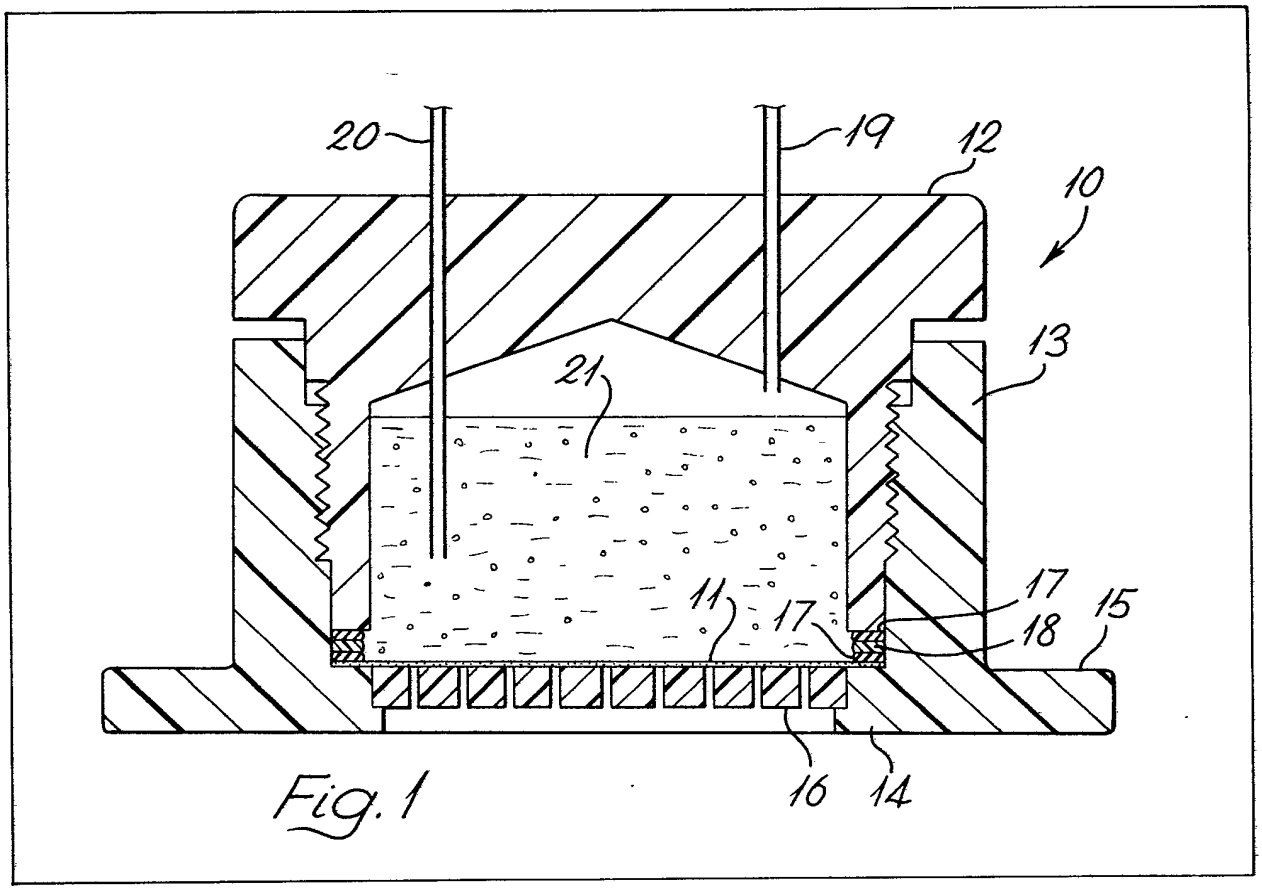

Fig. 1

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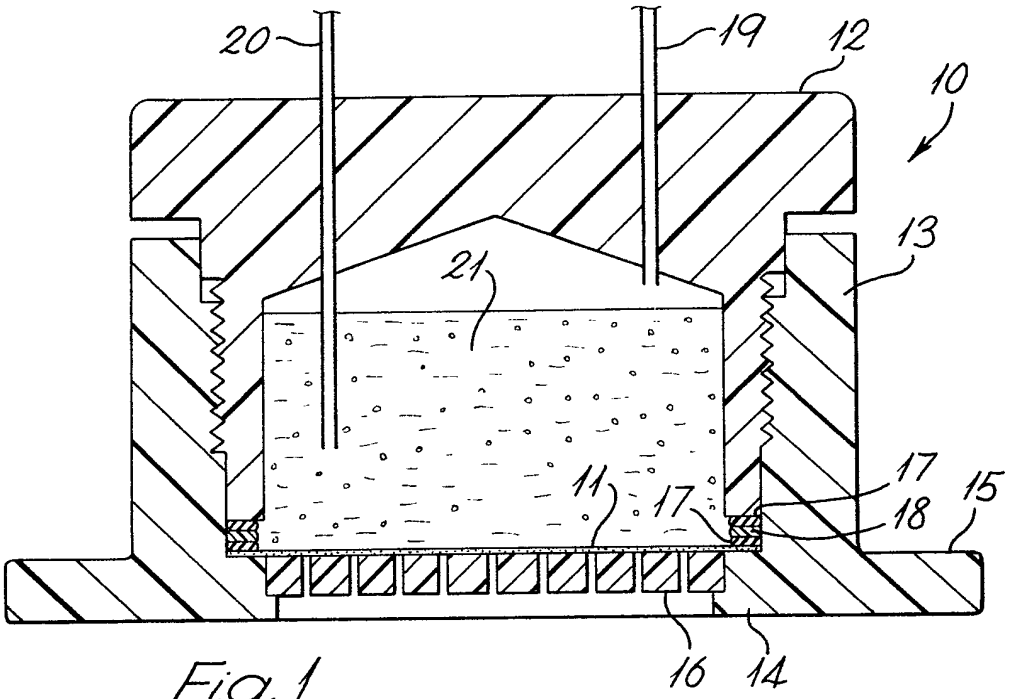

Fig. 1

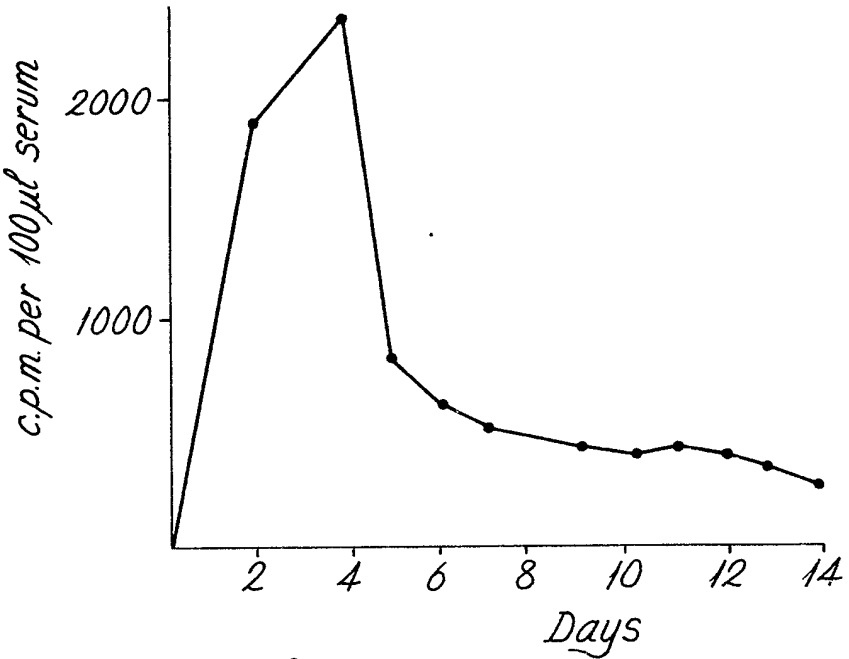

Fig. 2

SPECIFICATION

Medical treatment and apparatus therefor

Various proposals have been made for the production from living cells, modified to abnormal hybrid forms, of monoclonal antibodies specific for tumours, and for the use of such antibodies in diagnostic, monitoring and therapeutic applications. However difficulties can arise in such applications.

One difficulty can arise from the fact that the antibodies are commonly short-lived and this is disadvantageous in relation to the time necessary for the separation and other preparation thereof appropriate to the relevant application. Another difficulty arises from the fact that the applications commonly involve intermittent extracorporeal administration whereas, for therapeutic applications at least, benefit may well derive from continuous administration.

Clearly, similar consequences can arise with other proposals for the use of hybrid living cells adapted to produce sub-cellular material capable of affording beneficial activity in the body.

An object of the present invention is to improve this situation and to this end there is provided a subcutaneously implantable diffusion chamber housing the hybrid cells, the chamber having a wall defined by a membrane which, in vivo, inhibits the free diffusion therethrough of the cells but not subcellular material.

Following implantation of the chamber in a patient, the membrane allows outward diffusion of antibodies out or other active sub-cellular material into the patient, and inward diffusion from the host body of oxygen, nutrients or other sub-cellular material necessary to sustain the effectiveness of the encapsulated cells. At the same time, the membrane inhibits outward diffusion of the cells themselves and so obviates the risk that these may metastasise as a neoplastic growth or cause other undesired results in the patient. For these purposes the membrane should preferably allow passage of material of diameter up to about 0.2μm, but not higher.

Initial development of the invention has in fact involved the use of hybridoma cells to produce monoclonal antibodies specific for tumours, such cells being produced by fusing intratumoural lymphocytes from the subject tumour with a human myeloma line, and it is convenient to describe the invention further, by way of example, with reference to this development. Reference is also made to the accompanying drawings, in which:—

Figure 1 schematically illustrates in cross section a chamber used in initial development of the invention, and

Figure 2 graphically illustrates a result of use of the chamber of Figure 1.

The chamber of Figure 1 has a main body 10 of generally hollow circular cylindrical form having one end wall, which body is closed at its other end by a filter 11. The body is made in two parts 12 and 13, the former of which is of similar shape to that of the overall body, while the latter is of sleeve form for threaded engagement about the side wall of part 12. The sleeve part 13 has at its outer end a stepped inner flange 14 and an outer flange 15. The inner flange 14 supports a fenestrated filter support 16 and also, in association with the filter support, the filter 11. Around the periphery of the filter is located a succession of two O-rings 17 with a slip ring 18 therebetween, this succession being sealingly held, together with the filter, between the free end of the side wall of part 12 and the flange 14 when the chamber is assembled.

Remaining structural features of the chamber comprise inlet and outlet cannulae 19 and 20 projecting through the end wall of part 12 into and outwardly of the chamber.

In manufacture, the chamber 10 has been made up from materials and existing products of biologically acceptable forms. More specifically the body was made of a synthetic homopolymer, Delrin, the filter support is a 3cm diameter injection-moulded Millipore product, the filter is a Durapore product of nitro cellulose material and 0.22μm pore size, the O-rings and slip ring are existing products of rubber and nylon, and the cannulae are 21-gauge butterfly needles as used for intravenous injections. Clearly this construction can be varied.

Hybridoma cells housed in the chamber are denoted generally at 21, these cells having been produced as more particularly described in a communication entitled "Human Hybridomas from Malignant Gliomas" by K. Sikora et al in The Lancet, January 2, 1982,

Trial of this chamber has involved subcutaneous implantation, with the cannulae projecting transcutaneously outwardly into the upper anterior abdominal wall of a terminal patient, now deceased, with recurrent glioma. The procedure was carried out under local anaesthetic and the chamber secured by sutures passed through holes in the external flange 15. 10^8 human hybridoma cells previously prepared by the fusion of intratumoural lymphocytes from the patient's primary tumour were injected into the chamber in serum-free tissue culture medium. In addition, 10^7 cells which were pusle-labelled with 100μCi L-(4,5-3H) lysine monohydrochloride, specific activity 80Ci/mmol (Amersham International) were also injected into the chamber. Such cells were shown to release internally labelled immunoglobulin for up to 48 hours. Serum samples were collected from the patient at regular intervals following insertion of the chamber and trichloroacetic acid precipitable 3H counts determined by scintillation counting. The resultant counts are graphically illustrated in Figure 2 and clearly show tritiated monoclonal antibody release into the blood steam in the three days following installation of the pulse-labelled cells.

Examination during this trial indicated no problems arising from the chamber during a period of three months in which it remained in situ. Specifically, there was no evidence of infection or of an inflammatory response around the chamber. Also, in pre-trial testing, there was no evidence of any spread of hybridoma cells outside the chamber as judged by scanning electron microscope examination of the filter after incubating the chamber filled with 10^8 cells in tissue culture medium for fourteen

days.

CLAIMS

1. A subcutaneously implantable diffusion chamber housing hybrid living cells adapted to produce sub-cellular material capable of affording beneficial activity in the body, the chamber having a wall defined by a membrane which, in vivo, inhibits the free diffusion therethrough of said cells but not sub-cellular material.

2. A chamber according to Claim 1 wherein said cells are of hybridoma form adapted to produce monoclonal antibodies specific for tumours.

3. A chamber according to Claim 1 wherein said cells are formed by fusing intratumoural lymphocytes with a human myeloma line.

4. A chamber according to any preceding claim wherein said membrane only passes material of up to about 0.2μm diameter.

5. A chamber according to any preceding claim wherein said chamber comprises a hollowed body part and an annular body part, which parts are each made of a synthetic homopolymer and are threadably inter-engageable to retain therebetween a filter serving as said membrane.

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